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Modeling of the anti-cancer activity of 1, 4-naphthoquinone derivatives: A theoretical study

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ABSTRACT

1,4- Naphthoquinones moieties exhibit interesting chemical and biological characteristics, including anticancer activities. The aim of this study was to develop QSAR equations for a series of 1, 4- Naphthoquinone derivatives using multiple linear regression to model its potent and selective cytotoxicity against the tumorignic cell line L1210. Several electronic and molecular descriptors were derived for different classes of 1, 4 –naphthoquinones, using conceptual Density Functional theory. The QSAR result revealed the existence of a clear correlation between the cytotoxic activities of the test compounds and their electrophilic and lipophilic behavior, quantified by a set of electronic and physiochemical descriptors. The best-fit model involved the inclusion of an electrophilicity descriptor $E_{LUMO,}$ in conjunction with one of the two hydrophobicity descriptors, octanol-water partition coefficient (Log P) or polarizability (a), with R^2_{adj} ranging from 0.971-0.827.

Key words: Quantitative-structure-activity relationship, 1, 4- naphthoquinones, anti-cancer activity, density functional theory

INTRODUCTION

Due to recent advancement in the field of drug design and drug delivery, much progress has taken place in the treatment of cancer. However, cancer treatment still remain one of the challenging predicaments of the modern medical history. Normally, each cell coordinates with the others that compose tissues and organs of our body. One way that this coordination occurs is reflected in how your cells reproduce themselves. Normal cells in the body grow and divide for a period of time and then stop growing and dividing. Thereafter, they only reproduce themselves as necessary to replace defective or dying cells. Cancer occurs when this cellular reproduction process goes out of control. In other words, cancer is a disease characterized by uncontrolled, uncoordinated and undesirable cell division. Cancer is often thought of as an untreatable, unbearably painful and potentially a life-threatening illness.

Biological activities, structural properties and complex mode of action of quinones made them exceptional molecules in medicinal chemistry and therefore this class of molecules have become the focus of intense research interest [1] .These serve as bottom-line links in the various electron transport chains in the metabolic pathway, as DNA intercalates, bio-reductive alkylators of biomolecules and generators of reactive oxygen species (ROS). The quinones play various roles in normal biochemical processes, depending on their particular structure [2-6]. Their unique structural features, ease of reduction and ability to act as dehydrogenating agents are among the fundamental feature of their chemistry. Their redox cycling is attributed to their aromatic features[7,8]. They occurs abundantly in various families of plants[4,9,].1,4 Naphthoquinones being important member of quinones family, are used on large scale as raw material for pharmaceuticals, agrochemicals and other chemical industries. In folk medicine Naphthoquinones as plant extract was often employed for the treatment of various diseases [10,11] and several quinonoids isolated from these medicinal plants are under investigation for their role in anticancer activities [12]. Some of the biologically active 1,4 Naphthoquinones derivatives are rich in vitamin K and are known to be effective as blood clotters, antibacterials and antifungal[13-15]. 1,4-Naphthoquinones have been abundantly employed for years in domestic remedies and in various cosmetics products. Henna, which is popularly used for coloring skin and hair, containing lawsone (2- hydroxy-1,4-naphthoquinone) and is obtained from leaves of the Lawsonia alba[16]. Some naphthoquinone drugs have trypanocidal activities upon different trypanosomes and leishmania, which are responsible for several human diseases such as African sleeping sickness (Trypanosoma brucei rhodesiense and Trypanosoma brucei gambiense), Kala-azar (Leishmania donovani) and Chagas disease (Trypanosoma cruzi). These drugs include menadione (2 -methyl-1,4-naphthoquinone), plumbagin (2-methyl-5- hydroxy-1,4-naphthoquinone) and lapachol [2-hydroxy-3-(3- methyl-2-butenyl)-1,4-naphthoquinone] [17]. In general napthoquinones possess a diverse range of biological and pharmacological activities such as antibacterial [18,19], antifungal [20-21], anti-inflammatory [18,21-25], anti- thrombotic [26,27] antiplatelet [22-28], antiviral [18,29-31], anticancer [19,20,29,31-33], antiallergic [22-25,34], apopto- sis [35-36], lipoxygenase [37,38], radical scavenging [39] and anti-ringworm [18] activities.

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Excellent QSAR models can aid in understanding the drug action, toxicology and also in drug design process [40].QSAR models are employed for elucidating the mechanism of chemical –biological interaction in biomolecules especially in enzymes, bio-membrane and vital cell organelles [41]. QSAR study may save the cost and time in the course of developing a new drug and in the assessment of its toxicity as compared to other empirical procedures [42-44]. Due to their reliability and versatility, a large number of quantum chemical descriptors have been defined and applied successfully for developing QSAR models [45]. The density functional theory (DFT) is a powerful computational approach to investigate the precise electronic characteristic of molecular structure. Recent studies have shown that the quantum chemical descriptors based on the conceptual DFT method are better than those based on the semi-emperical method in establishing optimal QSAR model equations [46-55]. In this respect, quantitative structure-activity relationships (QSAR) have emerged as a promising tool toward the effective screening of potential drugs.

The objective of this work was to correlate the anticancer activity of a series of 1, 4-naphthoquinone compounds with some appropriate combination of electronic and structural descriptors and to ascertain, which combination of descriptors best quantify major molecular properties responsible for the

cytotoxicity of these 1,4- Naphthoquinones derivatives. In particular, highest occupied molecular orbital (HOMO)energies, lowest unoccupied molecular orbital (LUMO) energies, global hardness (η), softness (**S**), electronegativity (c), chemical potential (**μ**), electrophilicity index (w) electrofugality (**DE$_e$**), nucleofugality (**DE$_e$**), total energy(au) (**T**), molecular weight (**M**), octanol-water partition coefficient (**Log P**), molecular volume $(A^0)^3$ (**V**) and polarizability (a) were evaluated to describe reactivity and membrane permeability of various bioactive molecules. The experimental log 1/C (molar concentration of the compound leading to 50% net cell death) and Log P values (Table 1) used in this paper were taken from Song et al., Kyong-Up et al. and Verma [56-58].

Computational method

For all molecules studied here, the quantum chemical computations were performed using the Gaussian 03 quantum chemistry package [59]. The initial geometries were optimized by the DFT method by employing Becke's three-parameter hybrid functional (B3LYP) and 6-311G (d, p) basis set [52,60]. Moreover, the frequency calculations were performed to verify the optimized structure to be at an energy minimum. An In-house statistical package was used for regression analysis to develop the model QSAR equations. Anticancer activity in terms of log1/C was used as dependent variable and the quantifiers of hydrophobicity and electrophicity were used as the independent variables. Model adequacy was quantified with the r^2 value (squared coefficient of determination) adjusted for degrees of freedom. The number of observations (n), residual sum of squares (RSS) and Fisher statistic (F) were also reported.

Theoretical Background

Parr and co-workers have defined electrophilicity index (ω) as a measure of the decrease in energy due to the maximal transfer of electrons from donor to an acceptor molecule as [61];

$$w = \frac{\mu^2}{2\eta} \quad (1)$$

where μ and η are chemical potential and hardness respectively . Chemical potential [60],hardness [61,62] and softness [63] can be expressed in terms of ionization energy (I) and electron affinity (A) as ;

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{?(r)} \approx \frac{I+A}{2}, \quad \eta = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{u(r)} \approx \frac{I-A}{2} \quad \text{and} \quad s \approx \left(\frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{u(r)}\right)^{-1} \quad (2)$$

Employing Koopmans' approximation [64] , the ionization energy (**I**) and electron affinity (**A**) are the eigen value of the HOMO and LUMO with change of sign

$$\mathbf{I \tilde{\ } -E_{HOMO}} \qquad \mathbf{A \tilde{\ } - E_{LUMO}} \quad (3)$$

Two reactivity indices related to electrophilicity and nucleophilicity, as well as electrofugality and nucleofugality in terms of the reactant's first ionization potential and electron affinity have been introduced by Ayers et al. [65]. Electrofugality ΔE_e is defined as

$$D\mathbf{E_e = (\mu - \eta)^2 / 2\eta} \quad (4)$$

Nucleofugality ΔE_n is defined as

$$\mathbf{\Delta E_{n} = (\mu + \eta)^2 / 2\eta} \quad (5)$$

Polarizability is the measure of the change in a molecule's electron distribution in response to an applied electric field, which can also be induced by electric interactions with solvents or ionic reagents [66-68]. It represents a second order variable in energy;

$$\alpha_{a,b} = -(\partial^2 E / \partial F_a \, \partial F_b); \quad a, b = x, y, z$$

and is calculated as fallows

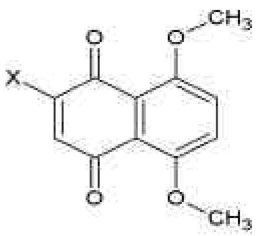
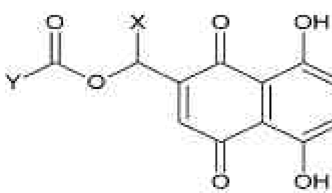
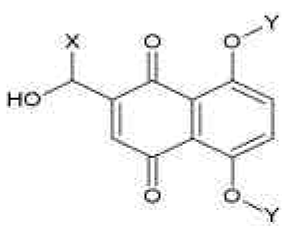
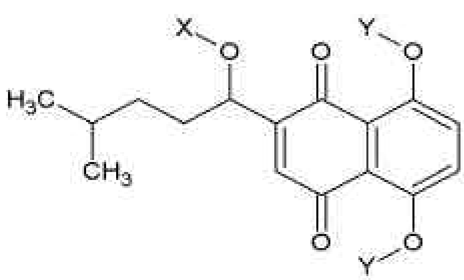
$$\langle a \rangle = 1/3\,(a_{xx} + a_{yy} + a_{zz}) \quad (6)$$

RESULT AND DISCUSSION

The main aim of this work was to correlate the biological activity of a series of 1, 4- Naphthoquinones with some appropriate structural and electronic descriptors to describe reactivity and membrane permeability of various 1,4-Naphthoquinones derivatives with respect to their cytotoxicity for cancer cells. The quantum chemical descriptors like LUMO energy, HOMO energy, ionization energy, electron affinity, chemical potential, hardness, softness, electrophilicity, polarizability etc., calculated from optimized geometries using equations 1-6, of a series of 1, 4- Naphthoquinones are given in Table 2. Various QSAR models have been developed in this work by employing physiochemical and quantum chemical descriptors as independent variables and log1/C as dependent variable. The general regression equations of the models constructed for the derivatives using one descriptor are given in Table 3. From our preliminary calculations, it becomes clear that among the set of calculated quantum chemical descriptors, only E_{LUMO}, μ and ω are the main independent descriptors contributing to the cytotoxicity character of all the four derivative classes, as indicated from the R^2_{adj} values of the QSAR equations. In case 2-X-5, 8-Dimethoxy-1,4 Naphthoquinones derivatives, using E_{LUMO}, μ and ω show better results as indicated by their corresponding R^2_{adj} values (see Table 3) . For 2-[CHX(OCOY)]-5,8-Dihydroxy-1,4 Naphthoquinones, using E_{LUMO}, Log P , α as independent variables in the model give better results as indicated by their corresponding R^2_{adj} values, whereas, the regression equation obtained by using electrophilicity index (ω) shows poor result in case of this class of naphthoquinones, as is evident from the R^2_{adj} value (0.694). In case of 2-[CH (OH)X]-5,8-$(OY)_2$-1,4 Naphthoquinones derivatives, model equations obtained by using E_{LUMO} and μ show good result as reflected from their R^2_{adj} values (0.825, and 0.780 respectively). However, the regression equations obtained by using (ω) or Log P show poor result in case of this class as indicated by the corresponding R^2_{adj} values (0.694 and 0.287respectively). For 2-[CH (OH)X]-5,8-$(OY)_2$-1,4 Naphthoquinones, the one parameter model equation obtained by using E_{LUMO} shows better result as indicated by the R^2_{adj} value (0.879), but the regression equation obtained by using electrophilicity index (ω) shows poor result as compared to E_{LUMO} in case of this class. Employing log P and α as the descriptors of lipophilicity of these derivatives also show good results, except in case of 2-[CH (OH)X]-5,8$(OY)_2$-1,4naphthoquinones.

In order to test whether a combination of conceptual density functional theory (DFT) based descriptors like E_{LUMO}, μ, ω, and physio-chemical parameters like Log P and α provide a significant improvement in the QSAR models, two parameter regression analysis was performed on the test compounds. For 2-X-5,8-Dimethoxy-1,4 Naphthoquinones derivatives, two parameter regression equations using combination of E_{LUMO} and Log P give better results as compared to E_{LUMO} and α, with corresponding R^2_{adj} values as 0.971 and 0.897 respectively (see Figure1) . There is increase in both, the energy of LUMO and value of Log P, as hydrogen at ortho position of quinone ring is substituted by carbonyl derivatives ranging from formyl to dodecanal groups. This may be due to the fact that the hydrophobic character of the molecule increases with the increase in length of the methyl chain. However, in case of 2-[CHX(OCOY)]-5,8-Dihydroxy-1,4 Naphthoquinones derivatives, the two parameter regression equations using a combination of E_{LUMO} and Log P show comparable results to those employing E_{LUMO} and α (see Figure 2). The substitution on the side chain of quinone ring does have little effect on Log P values, but a significant effect on E_{LUMO} and polarizability changes. In case of 2-[CH(OH)X]-5,8-$(OY)_2$-1,4 Naphthoquinones derivatives, the two parameter regression equations using a combination of E_{LUMO} and Log P gives poor results as compared to E_{LUMO} and α as shown in Figure 3. Substitution occurs both on the phenol as well as on the side chain of quinone ring containing a hydroxyl group, which may result in decrease in the energy of lowest unoccupied molecular orbital, but an overall increase in

Table 1: 1, 4-Naphthoquinone derivatives (1-46) with Log I/C units and Clog P used in the present study

Comp. no.	General structure	X	Y	Compound	*Log 1/C	**Clog P
2-X-5,8-Dimethoxy-1,4 Naphthoquinones						
1		CHO	-	$C_{13}O_4H_9$	6.39	1.51
2		$COCH_3$	-	$C_{14}O_5H_{12}$	6.38	1.31
3		COC_2H_5	-	$C_{15}O_5H_{14}$	6.25	1.84
4		COC_3H_7	-	$C_{16}O_5H_{16}$	6.34	2.37
5		COC_4H_9	-	$C_{17}O_5H_{18}$	6.31	2.90
6		COC_5H_{11}	-	$C_{18}O_5H_{20}$	6.30	3.42
7		COC_6H_{13}	-	$C_{19}O_5H_{22}$	6.28	3.95
8		COC_7H_{15}	-	$C_{20}O_5H_{24}$	6.11	4.48
9		COC_8H_{17}	-	$C_{21}O_5H_{26}$	5.94	5.01
10		COC_9H_{19}	-	$C_{22}O_5H_{28}$	5.80	5.54
11		$COC_{10}H_{21}$	-	$C_{23}O_5H_{30}$	5.66	6.07
12		$COC_{12}H_{25}$	-	$C_{25}O_5H_{34}$	5.61	7.13
2-[CHX(OCOY)]-5,8-Dihydroxy-1,4 Naphthoquinones						
13		C_5H_{11}	CH_3	$C_{18}O_6H_{20}$	6.70	4.56
14		C_5H_{11}	C_5H_{11}	$C_{22}O_6H_{28}$	6.59	6.68
15		C_5H_{11}	C_7H_{15}	$C_{24}O_6H_{32}$	6.32	7.73
16		C_5H_{11}	$CH_2CHCHCH_2CH_3$	$C_{22}O_6H_{26}$	6.28	6.39
17		i-C_5H_{11}	CH_3	$C_{18}O_6H_{20}$	6.82	4.43
18		i-C_5H_{11}	C_5H_{11}	$C_{22}O_6H_{28}$	6.11	6.55
19		i-C_5H_{11}	C_7H_{15}	$C_{24}O_6H_{32}$	5.92	7.60
20		i-C_5H_{11}	$CH_2CHCHCH_2CH_3$	$C_{22}O_6H_{26}$	6.59	6.26
21		C_9H_{19}	CH_3	$C_{22}O_6H_{28}$	7.52	6.68
22		C_9H_{19}	C_5H_{11}	$C_{26}O_6H_{36}$	5.96	8.79
23		C_9H_{19}	C_7H_{15}	$C_{28}O_6H_{40}$	5.72	9.85
24		C_9H_{19}	$CH_2CHCHCH_2CH_3$	$C_{26}O_6H_{34}$	5.87	8.51
2-[CH(OH)X]-5,8-(OY)$_2$-1,4 Naphthoquinones						
25		C_4H_9	CH_3	$C_{16}O_5H_{17}$	6.52	2.91
26		C_5H_{11}	CH_3	$C_{17}O_5H_{19}$	6.05	3.44
27		i-C_5H_{11}	CH_3	$C_{17}O_5H_{19}$	7.22	3.63
28		C_7H_{15}	CH_3	$C_{19}O_5H_{23}$	5.54	4.50
29		C_9H_{19}	CH_3	$C_{21}O_5H_{27}$	5.43	5.55
30		$C_{12}H_{25}$	CH_3	$C_{24}O_5H_{33}$	5.37	7.14
31		C_4H_9	H	$C_{15}O_5H_{15}$	6.85	3.13
32		C_5H_{11}	H	$C_{16}O_5H_{17}$	7.00	3.66
33		i-C_5H_{11}	H	$C_{16}O_5H_{17}$	6.77	3.53
34		C_7H_{15}	H	$C_{18}O_5H_{21}$	6.70	4.72
35		C_9H_{19}	H	$C_{20}O_5H_{25}$	6.52	5.77
36		$C_{12}H_{25}$	H	$C_{23}O_5H_{31}$	6.10	7.36
2-[CH(OX)(i-C_5H_{11})]-5,8-(OY)$_2$-1,4 Naphthoquinones						
37		CH_3	CH_3	$C_{18}O_5H_{21}$	6.22	2.45
38		C_2H_5	CH_3	$C_{19}O_5H_{24}$	7.52	2.79
39		C_5H_{11}	CH_3	$C_{22}O_5H_{29}$	5.17	4.11
40		i-C_5H_{11}	CH_3	$C_{22}O_5H_{29}$	5.19	4.13
41		C_7H_{15}	CH_3	$C_{24}O_5H_{34}$	5.12	4.95
42		CH_3	H	$C_{17}O_5H_{19}$	6.80	1.93
43		C_2H_5	H	$C_{18}O_5H_{21}$	6.89	2.26
44		C_5H_{11}	H	$C_{21}O_5H_{27}$	6.08	3.58
45		i-C_5H_{11}	H	$C_{21}O_5H_{27}$	6.25	3.55
46		C_7H_{15}	H	$C_{23}O_5H_{31}$	5.69	4.42

* ref. 57, 58 **ref. 59

polarizability of the molecules. In case of 2-[CH(OX)(i-C_5H_{11})]-5,8-(OY)$_2$-1,4 Naphthoquinones derivatives, the two parameter regression equation using a combination of E_{LUMO} and Log P gives comparable results as compared to E_{LUMO} and α (R^2_{adj} values as 0.917 and 0.900 respectively) as shown in Figure 4. The derivatives are formed by the substitution of alkyl groups on the side chain of the Naphthoquinone ring, which may be responsible for the increase of hydrophobic character without much effect on the polarizability of derivative.

These results are in good agreement with the earlier works [69] which show that the E_{LUMO} influence the half wave potential and thus, the cytotoxic activity of substituted 1,4-naphthoquinones and 1,4 quinones. The antitumor activity of the Naphthoquinones increases as the ease of reduction increase or decrease from a point of minimum activity. The 1,4-naphthoquinone derivatives contains two carbonyl groups which are possibly responsible for their biological activity because of their ability to accept one or two electrons to form the corresponding anion. The quantum chemical descriptors like, LUMO energy and electrophilic index (ω) both describe electrophilic reactivity. The E_{LUMO} is directly related with the electron affinity of a molecule and as such characterizes the extent of the molecules to be

Table 2: Calculated HOMO energies, LUMO energies, ionization energies, electron affinities, electronegativities, hardness, softness, chemical potential, total energy and polarizability of compounds

Comp No.	*Exp.	**Cal Log P	HOMO (au)	LUMO (au)	I(eV)	A(eV)	μ(eV)	x(eV)	h(eV)	S(eV)	w(eV)	E(au)	a (au)
1	6.39	1.51	-0.2554	-0.1319	6.95	3.59	-5.27	5.27	1.68	0.298	8.266	-877.57	59.65
2	6.38	1.31	-0.2572	-0.1305	7.00	3.55	-5.28	5.28	1.73	0.290	8.065	-916.99	61.15
3	6.25	1.84	-0.2484	-0.1227	6.76	3.34	-5.05	5.05	1.71	0.292	7.457	-956.11	62.67
4	6.34	2.37	-0.2561	-0.1301	6.97	3.54	-5.26	5.26	1.72	0.292	8.051	-995.64	64.15
5	6.31	2.90	-0.2561	-0.1290	6.97	3.51	-5.24	5.24	1.73	0.289	7.936	-1034.96	65.62
6	6.30	3.42	-0.2558	-0.1301	6.96	3.54	-5.25	5.25	1.71	0.292	8.059	-1074.28	67.14
7	6.28	3.95	-0.2572	-0.1286	7.00	3.50	-5.25	5.25	1.75	0.286	7.875	-1113.61	68.62
8	6.11	4.48	-0.2576	-0.1275	7.01	3.47	-5.24	5.24	1.77	0.282	7.756	-1152.93	70.09
9	5.94	5.01	-0.2492	-0.1213	6.78	3.30	-5.04	5.04	1.74	0.287	7.299	-1192.01	71.63
10	5.80	5.54	-0.2352	-0.1150	6.40	3.13	-4.77	4.77	1.64	0.306	6.943	-1231.33	73.15
11	5.66	6.07	-0.2345	-0.1154	6.38	3.14	-4.76	4.76	1.62	0.309	6.993	-1270.65	74.65
12	5.61	7.13	-0.2323	-0.1147	6.32	3.12	-4.72	4.72	1.60	0.313	6.962	-1309.96	76.15
1	6.7	4.56	-0.2293	-0.1220	6.24	3.32	-4.78	4.78	1.46	0.342	7.825	-1149.35	67.57
2	6.59	6.68	-0.2286	-0.1216	6.22	3.31	-4.77	4.77	1.46	0.344	7.802	-1306.61	73.55
3	6.32	7.73	-0.2032	-0.1283	5.53	3.49	-4.51	4.51	1.02	0.490	9.971	-1387.56	76.82
4	6.28	6.39	-0.2271	-0.1205	6.18	3.28	-4.73	4.73	1.45	0.345	7.715	-1305.37	73.24
5	6.82	4.43	-0.2289	-0.1220	6.23	3.32	-4.78	4.78	1.46	0.344	7.835	-1149.34	67.44
6	6.11	6.55	-0.2223	-0.1143	6.05	3.11	-4.58	4.58	1.47	0.340	7.135	-1306.60	73.41
7	5.92	7.6	-0.2286	-0.1216	6.22	3.31	-4.77	4.77	1.46	0.344	7.802	-1385.24	76.39
8	6.59	6.26	-0.2212	-0.1132	6.02	3.08	-4.55	4.55	1.47	0.340	7.042	-1305.38	73.08
9	7.52	6.68	-0.2234	-0.1154	6.08	3.14	-4.61	4.61	1.47	0.340	7.229	-1306.62	73.58
10	5.96	8.79	-0.2223	-0.1143	6.05	3.11	-4.58	4.58	1.47	0.340	7.135	-1463.88	79.53
11	5.72	9.85	-0.2187	-0.1114	5.95	3.03	-4.49	4.49	1.46	0.342	6.904	-1542.51	82.5
12	5.87	8.51	-0.2216	-0.1132	6.03	3.08	-4.56	4.56	1.48	0.339	7.033	-1462.64	79.18
1	6.52	2.91	-0.2444	-0.1676	6.65	4.56	-5.61	5.61	1.05	0.478	15.032	-1035.95	66.00
2	6.05	3.44	-0.2260	-0.1591	6.15	4.33	-5.24	5.24	0.91	0.549	15.087	-1075.27	67.51
3	7.22	3.63	-0.2576	-0.1852	7.01	5.04	-6.03	6.03	0.99	0.508	18.427	-1075.26	67.37
4	5.54	4.5	-0.2006	-0.1132	5.46	3.08	-4.27	4.27	1.19	0.420	7.661	-1153.91	70.52
5	5.43	5.55	-0.1977	-0.1117	5.38	3.04	-4.21	4.21	1.17	0.427	7.574	-1232.54	73.49
6	5.37	7.14	-0.1893	-0.1113	5.15	3.03	-4.09	4.09	1.06	0.472	7.891	-1350.49	77.98
7	6.85	3.13	-0.2025	-0.1628	5.51	4.43	-4.97	4.97	0.54	0.926	22.871	-959.76	63.04
8	7.00	3.66	-0.2525	-0.1878	6.87	5.11	-5.99	5.99	0.88	0.568	20.386	-996.69	64.26
9	6.77	3.53	-0.2451	-0.1518	6.67	4.13	-5.40	5.40	1.27	0.394	11.480	-996.68	64.22
10	6.70	4.72	-0.2238	-0.1521	6.09	4.14	-5.12	5.12	0.98	0.513	13.417	-1075.32	67.25
11	6.52	5.77	-0.2234	-0.1514	6.08	4.12	-5.10	5.10	0.98	0.510	13.270	-1153.95	70.24
12	6.10	7.36	-0.2201	-0.1474	5.99	4.01	-5.00	5.00	0.99	0.505	12.626	-1271.90	74.70
1	6.22	2.45	-0.2407	-0.1503	6.55	4.09	-5.32	5.32	1.23	0.407	11.505	-1114.57	69.13
2	7.52	2.79	-0.2778	-0.1735	7.56	4.72	-6.14	6.14	1.42	0.352	13.274	-1153.89	70.60
3	5.17	4.11	-0.1999	-0.1161	5.44	3.16	-4.30	4.30	1.14	0.439	8.110	-1271.84	75.11
4	5.19	4.13	-0.1944	-0.1166	5.29	3.17	-4.23	4.23	1.06	0.472	8.452	-1271.84	75.02
5	5.12	4.95	-0.2418	-0.1125	6.58	3.06	-4.82	4.82	1.76	0.284	6.600	-1350.48	78.07
7	6.80	1.93	-0.2223	-0.1540	6.05	4.19	-5.12	5.12	0.93	0.538	14.094	-1036.00	65.86
8	6.89	2.26	-0.2216	-0.1631	6.03	4.44	-5.23	5.23	0.80	0.628	17.194	-1075.32	67.36
9	6.08	3.58	-0.2216	-0.1496	6.03	4.07	-5.05	5.05	0.98	0.510	13.011	-1193.27	71.85
10	6.25	3.55	-0.2187	-0.1536	5.95	4.18	-5.07	5.07	0.89	0.565	14.494	-1193.20	71.89
11	5.69	4.42	-0.2198	-0.1466	5.98	3.99	-4.99	4.99	1.00	0.503	12.488	-1271.84	74.85

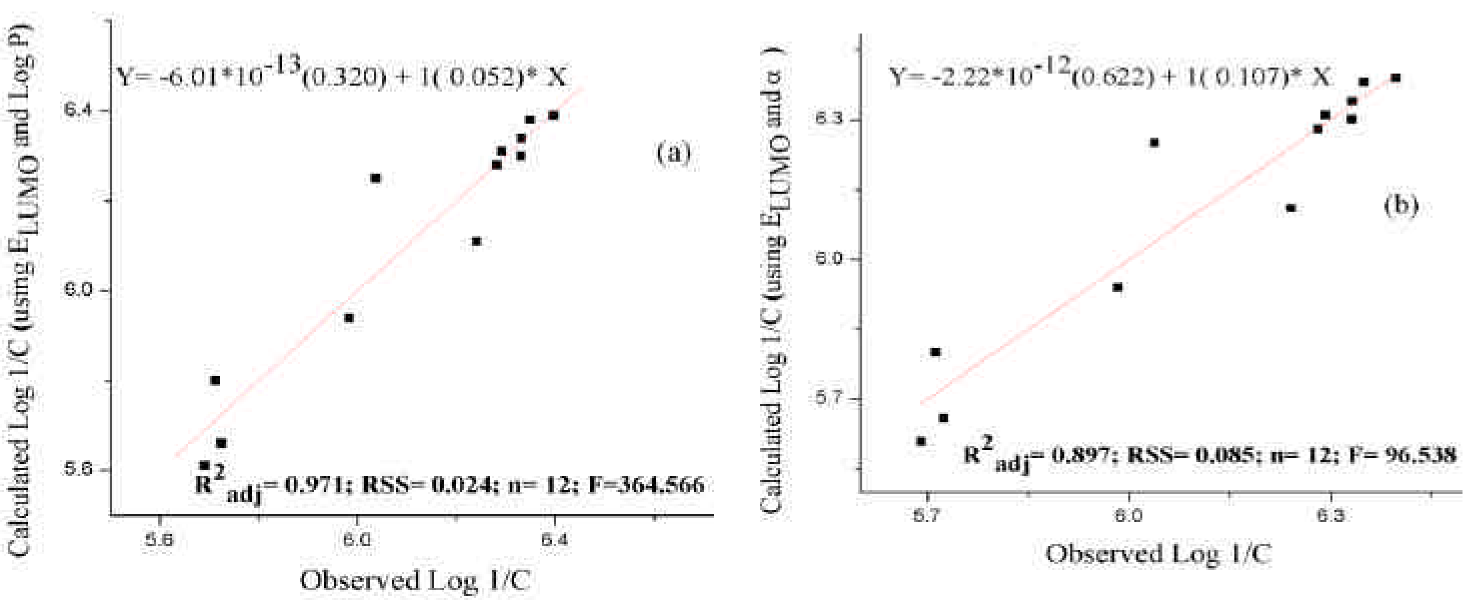


Figure 1: Observed and calculated Log 1/C values (a) using E_{LUMO} and log P descriptors and (b) using E_{LUMO} and log P descriptors in a two parameters regression model, for a2-X-5,8-Dimethoxy-1,4 Naphthoquinone derivatives

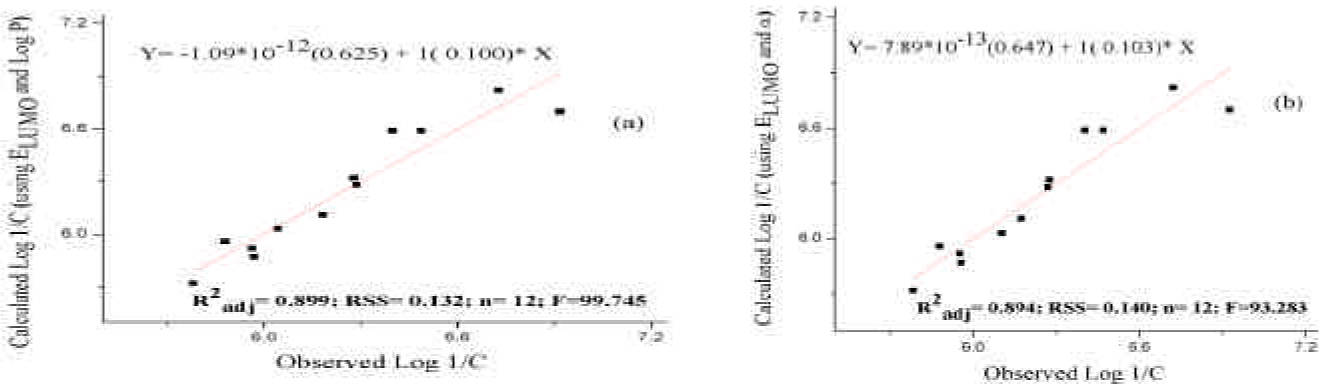


Figure 2: Observed and calculated Log 1/C values (a) using E_{LUMO} and log P descriptors and (b) using E_{LUMO} and log P descriptors in a two parameters regression model, for 2-[CHX(OCOY)]-5,8-Dihydroxy-1,4 Naphthoquinone derivatives

Table 3: General regression equations using one and two parameter obtained by total regression of compounds.

Equations	R^2	RSS	F
2-X-5,8-Dimethoxy-1,4 Naphthoquinones			
-0.983 HOMO -0.564	0.8368	0.1344	57.4151
1.516E_{LUMO} + 0.968	0.8959	0.0857	95.6911
-1.215μ - 0.075	0.8780	0.1005	80.1805
0. 557ω + 1.092	0.8757	0.1024	78.4769
-0.144Log P + 6.649	0.8551	0.1194	65.9151
-0.0486 α + 9.417	0.8231	0.1457	52.1856
-1.812 E_{LUMO} – 0.069 log P + 3.284	0.9706	0.0241	346.658
0.320 ω - 0.0713Log P + 3.944	0.9557	0.0365	238.597
-0.707 μ - 0.074 log P + 2.795	0.9750	0.0210	431.372
-1.887E_{LUMO} - 0.138 α+ 0.768	0.8967	0.1291	87.307
0.345ω + 0.022 α + 05.016	0.9366	0.0522	163.629
-0.638 μ + 0.276 α + 0.756	0.8966	0.0851	96.364
2-[CHX(OCOY)]-5,8-Dihydroxy-1,4 Naphthoquinones			
-1.021 HOMO+ 0.024	0.6391	1.4434	20.4833
-1.995E_{LUMO} – 0.138	0.8457	0.2034	61.2741
-1.861 μ + 2.399	0.6873	0.4122	25.1815
0.491 ω + 2.564	0.6946	0.4026	26.0155
-0.199LogP + 7.660	0.7887	0.2785	42.0579
-0.072α + 11.615	0.7759	0.2951	39.1027
-1.257 E_{LUMO} – 0.090 log P + 2.862	0.8997	0.1321	99.7454
0.226 ω - 0.132Log P + 5.49	0.8589	0.1860	67.9503
-0.787μ - 0.135log P + 3.555	0.8407	0.2099	59.0714
-1.298 E_{LUMO} – 0.031 α + 4.406	0.8935	0.1404	93.2831
0.236 ω - 0.046 α + 7.981	0.8551	0.1909	65.9198
-0.784 μ - 0.048 + 6.229	0.8237	0.2324	52.3770
2-[CH(OH)X]-5,8-(OY)$_2$-1,4 Naphthoquinones			
-0.812HOMO + 1.394	0.6001	1.5997	17.5055
-0.813E_{LUMO} + 3.017	0.8248	0.7010	52.7692
-0.881 μ + 1.861	0.7803	0.8789	40.0609
0.105ω + 4.887	0.6424	1.4304	20.7612
-0.245Log P + 7.471	0.2872	2.8513	5.4317
-0.108 α + 13.837	0.5954	1.6183	17.1894
-0.781 E_{LUMO} – 0.024 log P + 3.262	0.8272	0.6910	53.6717
0.092ω - 0.067log P + 5.373	0.6614	1.3545	22.4859
-0.828μ - 0.036 log P + 2.294	0.7858	0.8570	41.3423
-0.642 E_{LUMO} – 0.036 α + 6.200	0.8597	0.5611	68.4190
0.066 ω - 0.057 α + 9.356	0.7305	1.0782	30.8094
-0.654 μ - 0.044 a + 6.084	0.8398	0.6450	58.2174
2-[CH(OX)(i-C_5H_{11})]-5,8-(OY)$_2$-1,4 Naphthoquinones			
-0.800 HOMO + 1.173	0.3183	3.6288	5.2029
-1.339 E_{LUMO} + 0.859	0.8791	0.6435	66.4508
-1.342 μ - 0.654	0.7499	1.3312	27.9898
0.201 ω + 3.696	0.6154	2.0474	15.4005
-0.664 Log P + 8.361	0.6421	1.9054	17.1447
-0.173α + 18.556	0.6254	1.9939	16.0283
-1.102 E_{LUMO} – 0.046 log P + 5.109	0.9167	0.4437	99.9796
0.108 ω - 0.098 log P + 11.895	0.7465	1.3495	27.5009
-0.948 μ - 0.102 log P + 8.682	0.9251	0.3987	112.1444
-1.050 E_{LUMO} – 0.220 α + 2.742	0.9007	0.6786	62.5995
0.111ω - 0.402a + 6.148	0.7002	1.5963	22.0185
-0.928 μ - 0.385 α + 2.747	0.9356	0.34265	131.8223

Table 4: Observed and Calculated values obtained from using E_{LUMO}, w, Log P and a

Com No.	Exp.	E_{LUMO} Log P	D	E_{LUMO} a	D	w Log P	D	w a	D
1	6.39	6.452	0.062	6.397	0.007	6.482	0.092	6.518	0.128
2	6.38	6.429	0.049	6.349	-0.031	6.433	0.053	6.415	0.035
3	6.25	6.201	-0.049	6.037	-0.213	6.199	-0.051	6.170	-0.080
4	6.34	6.346	0.006	6.332	-0.008	6.350	0.010	6.342	0.002
5	6.31	6.282	-0.028	6.292	-0.018	6.275	-0.035	6.269	-0.041
6	6.30	6.273	-0.027	6.331	0.031	6.276	-0.024	6.277	-0.023
7	6.28	6.200	-0.080	6.281	0.001	6.179	-0.101	6.179	-0.101
8	6.11	6.136	0.026	6.241	0.131	6.102	-0.008	6.105	-0.005
9	5.94	5.944	0.004	5.984	0.044	5.917	-0.023	5.912	-0.028
10	5.80	5.752	-0.048	5.712	-0.088	5.764	-0.036	5.754	-0.046
11	5.66	5.724	0.064	5.724	0.064	5.741	0.081	5.737	0.077
12	5.61	5.632	0.022	5.691	0.081	5.653	0.043	5.692	0.082
13	6.70	6.917	0.217	6.925	0.225	6.872	0.172	6.887	0.187
14	6.59	6.398	-0.192	6.403	-0.187	6.354	-0.236	6.359	-0.231
15	6.32	6.278	-0.042	6.276	-0.044	6.197	-0.123	6.188	-0.132
16	6.28	6.286	0.006	6.270	-0.010	6.298	0.018	6.275	-0.005
17	6.82	6.727	-0.093	6.722	-0.098	6.749	-0.071	6.747	-0.073
18	6.11	6.183	0.073	6.173	0.063	6.239	0.129	6.228	0.118
19	5.92	5.963	0.043	5.951	0.031	5.987	0.067	5.970	0.050
20	6.59	6.486	-0.104	6.469	-0.121	6.502	-0.088	6.478	-0.112
21	7.52	5.879	-1.641	5.879	-1.641	5.871	-1.649	5.867	-1.653
22	5.96	5.780	-0.180	5.783	-0.177	5.746	-0.214	5.744	-0.216
23	5.72	5.969	0.249	5.956	0.236	6.077	0.357	6.059	0.339
24	5.87	6.043	0.173	6.103	0.233	6.019	0.149	6.107	0.237
25	6.52	6.752	0.232	6.748	0.228	6.567	0.047	6.584	0.064
26	6.05	6.559	0.509	6.546	0.496	6.537	0.487	6.502	0.452
27	7.22	7.109	-0.111	7.006	-0.214	6.833	-0.387	6.730	-0.490
28	5.54	5.557	0.017	5.635	0.095	5.777	0.237	5.840	0.300
29	5.43	5.500	0.070	5.503	0.073	5.698	0.268	5.665	0.235
30	5.37	5.453	0.083	5.335	-0.035	5.620	0.250	5.430	0.060
31	6.85	6.645	-0.205	6.771	-0.079	7.279	0.429	7.270	0.420
32	7.00	7.163	0.163	7.163	0.163	7.013	0.013	7.037	0.037
33	6.77	6.401	-0.369	6.536	-0.234	6.196	-0.574	6.451	-0.319
34	6.70	6.379	-0.321	6.433	-0.267	6.295	-0.405	6.406	-0.294
35	6.52	6.338	-0.182	6.313	-0.207	6.211	-0.309	6.226	-0.294
36	6.10	6.213	0.113	6.081	-0.019	6.044	-0.056	5.929	-0.171
37	6.22	6.498	0.278	6.426	0.206	6.435	0.215	6.328	0.108
38	7.52	7.085	-0.435	7.052	-0.468	6.494	-1.026	6.375	-1.145
39	5.17	5.156	-0.014	5.126	-0.044	5.393	0.223	5.372	0.202
40	5.19	5.164	-0.026	5.143	-0.047	5.423	0.233	5.418	0.228
41	5.12	4.866	-0.254	4.879	-0.241	4.889	-0.231	4.917	-0.203
42	6.80	6.718	-0.082	6.687	-0.113	6.931	0.131	6.930	0.130
43	6.89	6.904	0.014	6.890	0.000	7.141	0.251	7.118	0.228
44	6.08	6.228	0.148	6.278	0.198	6.148	0.068	6.223	0.143
45	6.25	6.351	0.101	6.398	0.148	6.324	0.074	6.379	0.129
46	5.69	5.959	0.269	6.052	0.362	5.752	0.062	5.871	0.181

attacked by nucleophiles and have been reported to be important in radical reactions. Although both (ω) and E_{LUMO} parameterize the electrophilic reactivity, the difference in their effectiveness in the QSAR models may be

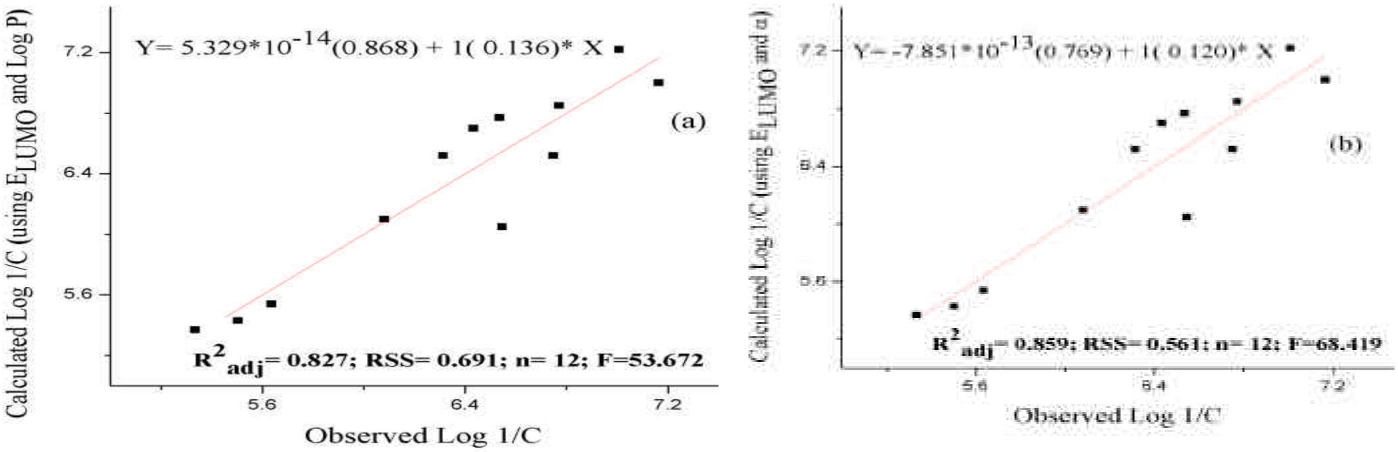


Figure 3: Observed and calculated Log 1/C values (a) using E_{LUMO} and log P descriptors and (b) using E_{LUMO} and log P descriptors in a two parameters regression model, for 2-[CH(OH)X]-5,8-$(OY)_2$-1,4 Naphthoquinones derivatives.

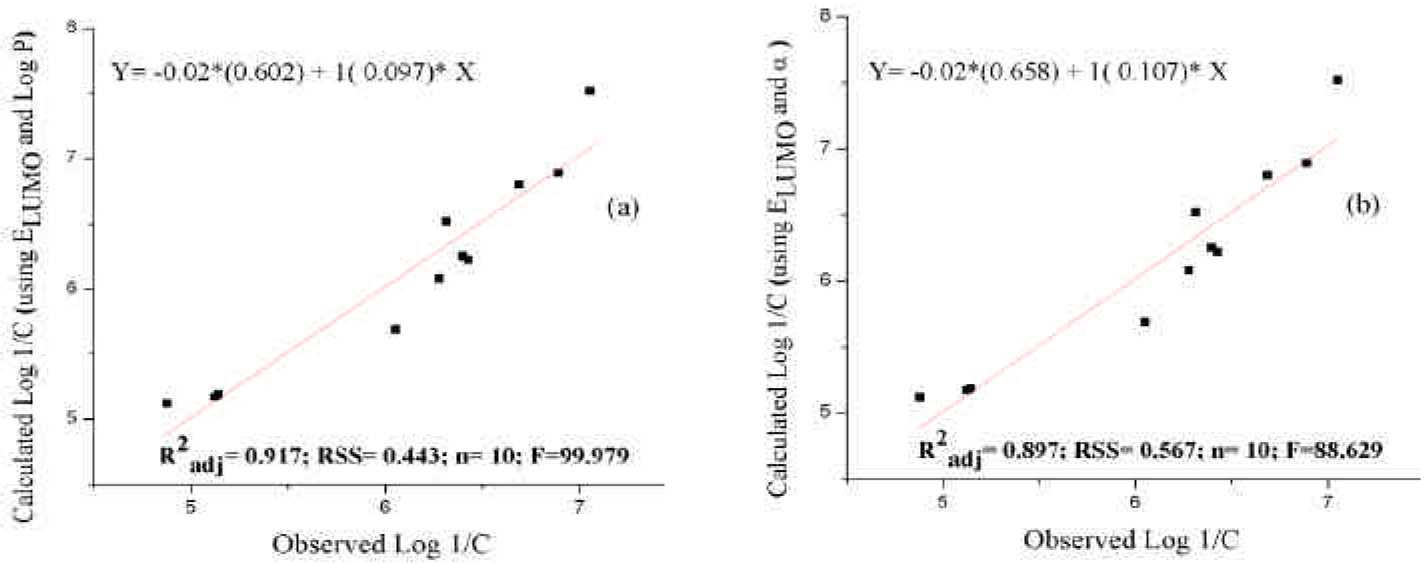


Figure 4: Observed and calculated Log 1/C values (a) using E_{LUMO} and log P descriptors and (b) using E_{LUMO} and log P descriptors in a two parameters regression model, for 2-[CH(OX)(*i*-C_5H_{11})]-5,8-$(OY)_2$-1,4 Naphthoquinone derivatives

attributed to the fact that the electrophilicity index (ω) is the measure of energy lowering associated with the amount of electron flow between two species (Parr et al.[61]), while as E_{LUMO} is directly related to electron affinity as per the Koopmans' theorm. The role of lipophilicity or hydrophobic character of a compound in its biological activity can be understood by the fact that the cell membranes are composed of phospholipids having hydrophobic tails which produce a very hydrophobic environment in the middle of the lipid bilayer. The octanol– water partition coefficient, here in represented as log P, is a descriptor for molecular lipophilicity and represents the ability of the molecules to cross the bio-membranes, particularly the blood–brain barrier and, therefore, encodes biouptake and availability of the Naphthoquinone molecules at the site of the cytotoxic action. The role of polarizability (α) in the anti-cancer activity of the Naphthoquinones was also a focus of our investigation. The electrons and nuclei in a molecule are mobile and free to move to a limited degree. Thus, small change in displacement can take place in polar and nonpolar molecules in the presence of small local electric fields, which results in a dipole being introduced in addition to permanent one that may already exist. Besides other effects, it may lead to change in solubility of a given compound at a given target site. The chemical potential refers to the measure of escaping tendency of electrons from equilibrium and it has been identified with the negative of electronegativity (x). Role of electrophilicity index (ω)and chemical potential(μ) can be assigned to the presence of hydroxyl groups at 5 and 8 positions, which allow the tautomerism and thus, cause the reduction in the electrophilic character of the Naphthoquinone ring. Due to the existence of resonance equilibrium state, the electron density will disperse over the ring, which result in change in electrophilicity and polarizability.

CONCLUSION

The primary focus of the present study was to develop the QSAR models using some appropriate structural and electronic descriptors to relate the chemical structure of various 1,4- Naphthoquinones to their cytotoxic activity for cancer cells. In view of the above results, we conclude that physico-chemical properties like Log P and α in conjunction with Quantum chemical descriptor like E_{LUMO} and ω can successfully be used for modeling the cytotoxic activity of 1,4- Naphthoquinones derivatives towards cancer

cells . These results will help the medicinal and pharma-chemical scientists in the design and predication of new derivatives with increased cytotoxicity activity.

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